EXERCISE, CARBON DIOXIDE AND CYSTIC FIBROSIS A PILOT STUDY

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EXERCISE, CARBON DIOXIDE AND CYSTIC FIBROSIS: A PILOT STUDY

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INTRODUCTION

Cystic fibrosis is apparently an inborn error of metabolism with widespread clinical and pathological effects. Its most intimate secrets, of specific cause and detailed mechanism, are still fast. The flux in concepts of this disease had lead to a lack of definition and uniformity. The biochemical changes in the exocrine glandular system are still speculative and controversial.

Effects to clarify the genetic characteristics of the disease have lead to the conclusion that it is probably recessive, and may or may not conform to Mendelian genetic principles. Orzalesi _et al_, 1963, found no significant abnormalities in sweat electrolytes, anamesis or pulmonary function in the parents of children with cystic fibrosis.[1]

The cardio-pulmonary complications of the disease often become the dominant determinants of its course as those with the disorder grow beyond infancy.[2] Therefore, as the disease progresses, the pulmonary manifestations assume a critical position in the therapeutic control of the disease.

The currently available laboratory tests of pulmonary function have not provided unequivocal indicators of cardio-pulmonary status or of changes in status[3, 4, 5]. In normals, the spirometric measurement of vital capacity may have a range of values of as much as $\pm$ 34%[6]. Polgar & Chernick (_op. cit._) found that variations in the longitudinal study of pulmonary functionwere generally independent of symptoms and therapy in chronic obstructive lung disease. Cook _et al_ (_op. cit._) found the ratio

of RV/TLC in patients with cystic fibrosis to have the best statistical correlation with their clinical rating system. Mitchell et al, 1964, analysed factors influencing prognosis in chronic obstructive broncho-pulmonary disease[7]. They found the RV/TLC of only "slight influence" in predicting or correlating with mortality and disability.

In addition, significant changes occur in the performance of any given individual on spirometric testing as a result of learning effect. The same can be said of the values obtained by different technicians testing the same individual, even with correction for the learning effect. Pulmonary function testing, though a product and a tool of the science, must constantly be interpreted with due regard for the art of the tester and the degree of cooperation of the subject.

The purpose of this inquiry, then, is to design and evaluate a test of cardio-pulmonary function which might provide a more sensitive measure than current methods.

Considerable effort has been spent in an attempt to define the basic pathophysiology of cystic fibrosis. The alterations of exocrine glandular secretions are widespread, whatever their site of secretion in the bodies of these patients. Certain complications of the disease can reasonably be explained on the basis of the marked increase in the viscosity of these secretions. These include: pancreatic enzymatic insufficiency secondary to obstruction of the pancreatic ductules; focal biliary cirrhosis secondary to intrahepatic biliary obstruction; recurrent pulmonary small-airway obstruction and peri-bronchiolar inflammatory reaction, leading to

atelectasis and recurrent pulmonary infection. In the older age group, the cardio-pulmonary problems usually far outweigh the digestive difficulties.

The airway obstruction, inflammation and recurrent infection may produce pulmonary hypertension and cor pulmonale and widespread destruction of lung tissue[8]. The consensus of those studying pulmonary function in cystic fibrosis is that there is no change in the total lung capacity. There is a volumetric and dynamic picture consistent with widespread airway obstruction, greater in expiration than inspiration.[1]

A prominent early characteristic of pulmonary involvement is atelectasis, which involves the right lung almost exclusively[9]. The net result is a loss of the normal distribution and mixing of inspired air[10]. However, there is often no consequent change in the blood gas values for CO_2 and O_2.

From the preceding, it comes apparent that cystic fibrosis is marked by frequent exacerbations in the pulmonary arena, characterized early by acute diffuse small airway obstruction, peri-bronchiolar inflammation, bronchiolar thickening, early fibrosis and recurrent infection. Progression and chronicity bring further fibrosis, emphysema, and intermittent hypoxemia with pulmonary hypertension. Hypercapnea and respiratory acidosis, with and without compensation or complications, and right heart failure may mark the disease.

All of the above pathological consequences could be prevented if effective means could be found to bring the physical properties of the

viscid secretions back to normal. Many forms of therapy directed toward this end have been devised, on the basis of the *in vitro* characteristics of these secretions. Their therapeutic efficiency can finally be judged only by *in vivo* demonstration of effectiveness. The need for techniques that can dependably measure changes produced by the disease and changes produced by therapy is obvious.

Procedures for the evaluation of cardio-pulmonary function have proliferated as a result. Many of these are very precise; yet all have their limitations. Measurement of carbon dioxide or oxygen in exhaled air or arterial blood can be very accurately performed. Frequently, the values in the resting state are entirely within normal limits in the face of significant disease. The discomfort and complications attendant on arterial puncture pose additional problems. An oxygen equilibration index, devised by Demuth *et al*, 1962, produced too many false positives.[3] The complicated interplay of cardiac and pulmonary and other factors, compensatory change in one area balancing destructive change in another, makes the interpretation of values obtained at rest difficult and at times misleading.

With due regard for the dangers of over-simplification, two broad categories emerge:

1. Parameters measurably effected by disease, which are, also, significantly influenced by factors unrelated to disease; ie., those requiring maximum patient cooperation in their measurement.

2. Parameters subject to tight homeostatic control. Compensatory

mechanisms, cardio-pulmonary, biochemical etc., keep these parameters within the normal range at rest. This is particularly true of carbon dioxide values; arterial, venous, and alveolar.

These conditions prompted a search for a test of cardio-pulmonary function which would accurately reflect the dynamic capacities of the system.

A number of factors led to the study of the profile of CO_2 output from the lungs in response to exercise. One of the primary functions of the cardio-pulmonary circuit is to maintain physiologic levels of carbon dioxide in the circulating blood. The gradient for oxygen is from without inward; that for carbon dioxide the reverse, since almost all of it arises from endogenous metabolic processes. The amount of CO_2 to be disposed of by the lungs can be increased by increasing the rate of some of these metabolic processes. The increased muscular activity of exercise is one of the most physiological means for achieving such an increase.

This study was based on the assumption that elimination of CO_2 by the lungs, if followed from rest, through moderate exercise, to equilibrium following exercise, might show a time course significantly different from the normal in patients with lung damage due to cystic fibrosis. The advantages, in addition to those enumerated above, were: an experimental protocol involving little patient discomfort, abundant material in exhaled gas for analysis, and accurate and proven methods for measurement of gaseous CO_2.

MATERIALS AND METHODS

The experimental protocol described below was designed entirely by the author, with the exception of the Scholander gas analysis of CO_2 and O_2.

The patients participating in this study were drawn from the population of cystic fibrosis patients under care of Dr. Vivian Tappan and the Chest Metabolic Clinic of the Yale-New Haven Community Hospital. They were fourteen in number, seven males from 5-11/12 to 16-5/12 years of age and seven females from 6-0/12 to 23-1/12 years of age.

Of the control group two were siblings of patients in the test, one a 15-7/12 year old female, (B.L.), the other a 10-1/12 year old male (D.M.). The other four were volunteers drawn from among the pre-operative admissions to the Yale-New Haven Ear , Nose, and Throat service for elective tonsil-adenoidectomies. Except for the hypertrophic lymphoid tissue bringing them to operation they were entirely well. All of the subjects tested had been going to school or working and came to testing directly from their usual activities.

Each subject rested in the laboratory for at least fifteen minutes before the first minute volume of exhaled air was collected.

The equipment used in the performance of this study was as follows:

Lanooy hyperbolic bicycle ergometer, 0-200/400 Watts

One-way 'J' valve, 1" ID

British cloth-covered corrugated tubing, 7", 1" ID

Rubber mouth-piece & sponge-rubber nose clamp

Aluminum "T" shape stop-cock, 3-way tap, 3/4" ID

Neoprene latex meteorological balloons, 30 L capacity

Precision Wet Test gas meter, Precision Sci. Co., 3L/rev.

Gas collecting tubes, glass, 125 ml

Gas sampling assembly, see fig. 1

Scholander gas analyser

Each subject was an hour or more post prandial. Each was instructed carefully in the techniques to be employed in the test. For each minute volume collected in the meteorological balloon, the nose clip was placed, the mouthpiece adjusted airtight, and the patient allowed fifteen to thirty seconds to wash out the efferent limb of the system. The three way tap on the stopcock was then turned to conduct the exhaled air into a previously wrung-out balloon. After the lapse of exactly one minute, the stopcock was returned to its initial position and the neck of the balloon was clamped with a rubber shielded Kelly clamp.

Within ten minutes of its collection, three litres of sample were fed through the wet test meter via the special connector (fig. 2) filling the connector with sample. The rubber section was clamped and disconnected from the meter. The vaccine bottle stopper was driven down over the nercury-filled sampling needle (fig. 3) and 150 ml of sample gas was admitted to the glass collecting bottle as the mercury was drained from it. The collecting bottle stopcocks were closed, the lower first and then the upper, to ensure that no pressure gradient existed with room air.

Fig. 1: gas sampling assembly; exploded view

Fig 2: Sampling Assembly; note vacuum bottle stopper

Fig. 3: Glass Collecting Bottle with Sampling Needle

The connector was lifted off the needle, returned to the wet test meter, and the remaining gas volume was measured. This procedure was used for all of the six gas samples taken from each subject.

Precautions were taken to prevent loss of sample volume and contamination with room air, including periodic tests of the integrity of the balloons.

Minute volume samples were taken from the subjects as follows:

1: at rest, after ten to fifteen minutes sitting quietly in the laboratory.

2: during the last minute of a six minute period of moderate exercise the work load being judged according to the capacities of each subject.

3: during the minute immediately following cessation of exercise.

4, 5, & 6: during the one minute intevals beginning 3, 7, and 19 minutes respectively following the cessation of exercise.

The six samples thus obtained were analysed from their gas collecting bottles on the same day. Using the transfer pipette and the Scholander gas analyser apparatus[11], (fig. 4), the percent concentration of CO_2 and O_2 of each sample was measured, and the minute volume of CO_2 calculated.

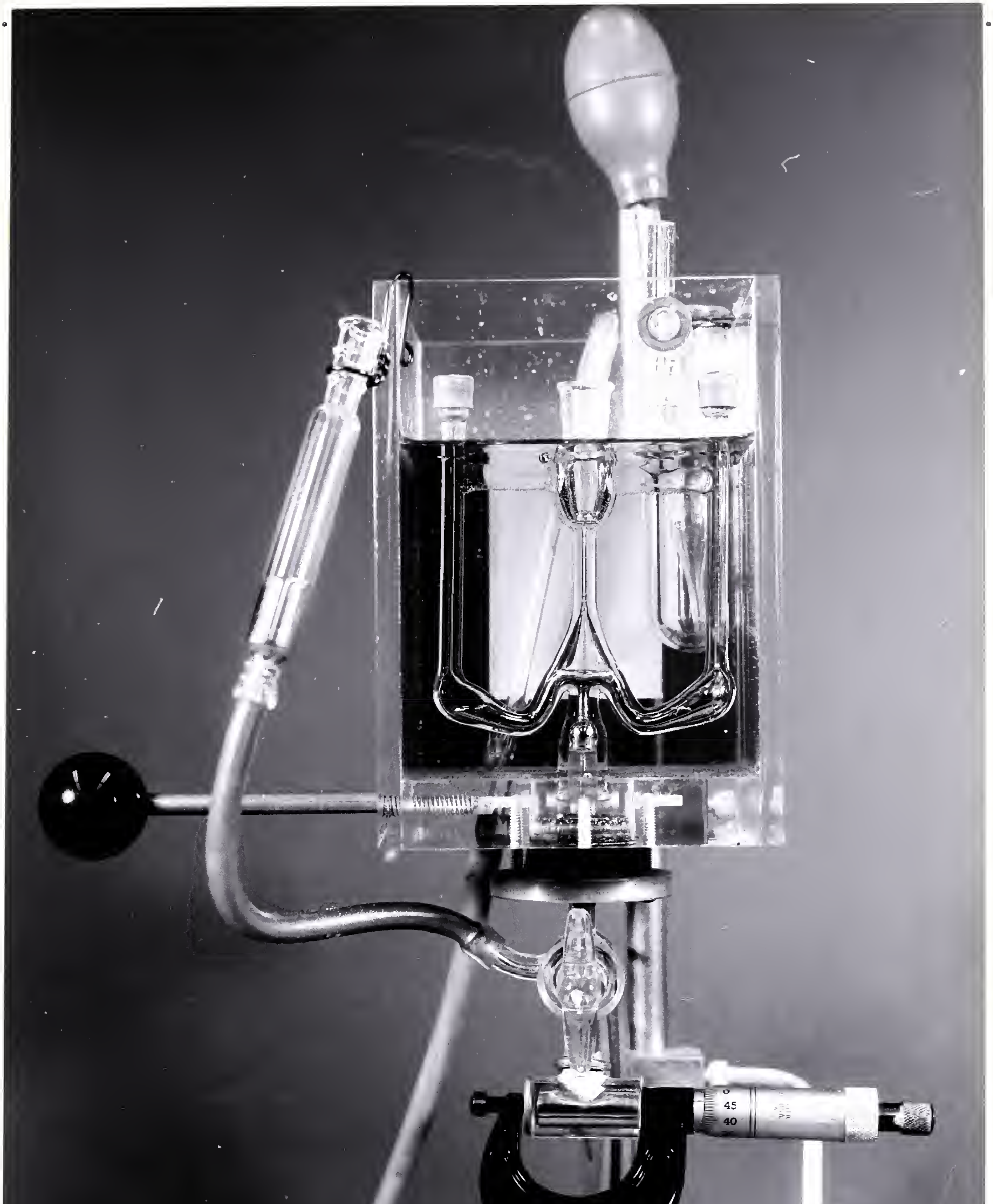


Fig. 4: Scholander Gas Analyzer

RESULTS

The protocol described above provided six values of CO_2 output in ml/min. for each subject. These values were processed to determine the time in minutes required for the $\dot{V}_{CO_2}$ to fall to halfway between the steady state $\dot{V}_{CO_2}$ of exercise and the average resting $\dot{V}_{CO_2}$. This time determination was made graphically on semilogarithmic ruled paper. $\dot{V}_{CO_2}$ was plotted logarithmically on the ordinate, and the midpoint in time of the minute during which the CO_2 was collected served as the abscissa coordinate. Three values of $\dot{V}_{CO_2}$ were entered. One, collected during minute 5 to minute 6 of exercise, is the steady state value referred to above. The second is from the minute volume collected immediately following exercise. The third is from the minute volume collected next in sequence. This was usually obtained starting three minutes after cessation of exercise. A best-fitting straight line was drawn with these three values, plotted on semi-logarithmic ruled paper. The resting $\dot{V}_{CO_2}$ is the average of the minute volume collected before exercise and that collected 19 minutes after exercise. The $\dot{V}_{CO_2}$ used to determine the 1/2 time was the average of the steady state exercise $\dot{V}_{CO_2}$ and the resting $\dot{V}_{CO_2}$, and the 1/2 time was read as the time at which the best-fitting straight line defined above crossed the 1/2 time $\dot{V}_{CO_2}$.

It was noted that the raw real CO_2 1/2 time tended to increase with age, necessitating some correction. In order to make the results of testing individuals of different ages comparable, the real CO_2 1/2 times

determined for the normal subjects were plotted versus age to the nearest month. A regression line was estimated and laid on the plot. Only after this was completed were the points representing the patients studied also plotted, as shown in fig. 8.

The regression line so determined was used to determine the predicted CO_2 1/2 time. For all the cystic fibrosis patients, the real 1/2 time, experimentally determined, and the predicted 1/2 time for a patient of that age, taken from the regression line, were compared yielding the % predicted 1/2 time for each patient.

A more refined analysis of the effects of exercise would have to establish a more rigid relationship between age and exercise load. A plot of 1/2 time versus exercise load was tried and did not appear to offer significant advantages.

One of the patients studied (M. L.) could not be exercised except at the lightest of exercise loads available (10 Kw). Her CO_2 response curve was so flat that her 1/2 time could not be determined with accuracy and she was omitted from the study. All of the other patients and all of the normal volunteers are included in the results.

In order to test the validity of the CO_2 1/2 time as an objective measurement, it was compared with several other available methods of evaluation.

The first of these is shown in fig. 9. A medically qualified observer (V. T.) with intimate and long-term aquaintance with each of the patients sorted each of the thirteen into one of three classes. These classes

formulated on the basis of overall capacities for physical activity. In class I were all those patients with no discernable difference from the normal population in their reaction to physical activity. Class II contained those known to have minimal limitation, or slight dyspnea on strenuous activity. In class III were those with moderate to severe limitation, dyspneic on restricted activity. Fig. 9 shows a plot of the % predicted 1/2 time for each of the four groups: six controls, six patients in class I, four in class II, and three in class III. The patient omitted (M. L.) fell in class III. The small numbers ajoining each point correspond to the kilowatt exercise load each individual sustained.

Comparisons were, also, made between the % predicted 1/2 time and several pulmonary function parameters. These were: RV/TLC (fig. 10), RV (fig. 11), VC (fig. 12), and FRC (fig. 13). All were expressed in terms of % of predicted value for those between age 5 and age 17, using the data of Helliesen *et al*[42]. The two individuals over 17 years of age (C. McM, a patient, and B.D., a control) were plotted relative to the normal values for the adult cardiopulmonary laboratory at this center.

The broken lines on figs. 9 through 13 represent the 100% levels for the ordinate and ascissa where appropriate, to facilitate interpretation.

The units used to indicate work load are written Kw. These units are unique to the Lanooy ergometer. They are not equivalent to kilowatts.

DISCUSSION

In discussing the findings of this exercise study it may be useful to set them against the backdrop of some of the general and specific information available about ventilation, CO_2 output, O_2 intake and exertion.

Foremost among the functions of the cardio-pulmonary unit are the maintenance of physiologic levels of oxygen, carbon dioxide and hydrogen ion concentration. In a normal young male oxygen intake is about 250 ml, CO_2 output is approximately 200 ml for a respiratory quotient of 0.8. In the face of severe stress, his O_2 intake may increase up to 22 times, and his CO_2 output as much as fifty times these levels. Functional reserve of this magnitude makes it possible to maintain normal resting values of P_{O_2} and P_{CO_2} in the arterial blood in spite of severe lung damage due to disease. For this reason, many authors have studied patients under some form of stress, hoping to delineate the extent of damage more accurately.

Consideration of these studies may be facilitated by review of some of the factors involved.

Acute hypoxia stimulates respiration only via the carotid and aortic chemoreceptors. Hypoxia without hypercapnia will not stimulate respiration until the $F_{I_{O_2}}$ drops to less than 14%, corresponding to an arterial P_{O_2} of less than 60 mm Hg. This is less true with chronic hypoxia.

Hypercapnia stimulates respiration both via the chemoreceptors and acting directly on the respiratory center. Any rise in the $F_{I_{CO_2}}$

produces a nearly linear rise in ventilation.

The inter-relationships of the O_2 and CO_2 levels on the stimulation of respiration are recognized but not clearly defined. Lowering the P_{O_2} of the blood enchances the response to any given P_{CO_2} and increases the sensitivity of the respiratory center to CO_2[12]. The respiratory center is also sensitive to H^+ concentration. The effect of CO_2 may depend on the subsequent formation of carbonic acid with the release of H^+.

Additional studies have compared the P_{CO_2} sensitivity of adults and infants[13], the capacity of man to store CO_2 on an acute basis[14], and the change in pH of the blood when the whole body is titrated with CO_2[15]. The results of these inquiries have leant support to current concepts of ventilatory chemistry, have served to clarify and extend them, and have provided some quantitative tools for their application. Their shortcoming has been their failure to provide clear and precise exposition of basic functional interrelationships.

Studies performed on man at rest have been more successful in this regard than studies on man exercising. One difficulty has been in identifying the specific mechanisms leading to the linear increase in ventilatory volume at increasing levels of external work. This increase is linear over a limited range; ie., not exceeding 70% of the maximum six minute work level of which the particular subject is capable[16]. Measurement of arterial lactic acid, P_{O_2}, P_{CO_2} and pH clearly eliminate these parameters from any measure of control in exercise. Within 30% of

this maximum work level, rises in lactic acid and H^+ concentration contribute to but do not supplant the basic stimulus to hyperpnea[17].

The ventilatory responses so easily demonstrable when exogenous CO_2 is used[18] are not cut of the same cloth as the ventilatory responses to exercise. Much work in this field has been directed toward isolating a servomechanistic loop seeking a homeostatic set point. This wo rk has been given added impetus by the demonstrated constancy of the arterial P_{CO_2}, and by the fact that manipulation of the P_{CO_2}, P_{O_2}, and pH give rise to activity that tends to restore these values toward normal. Perhaps Occam's razor has been applied here to aggressively. It seems realistic to accept two modes of operation for the respiratory center. One seems devoted to regulating the parameters to which detectors in the system are sensitive. The other is seemingly a higher order of function predicated on the unique capacities made available by the collective organized function of aggregations of nerve cells.

One of these aggregations, the respiratory center, seems to be so organized that it responds to muscular activity, among other things, and its response is such that significant change in the variables dependent on ventilation are prevented. Some of the tools of the discipline of electronic servomechanisms might be applied here with some profit. The diagram showin in fig. 7 is such an application. Before elaborating on this diagram some of the limitations imposed on formulating it must be pointed out and emphasized.

This diagram must not be interpreted as a direct translation of the function of the respiratory center into electronic circuitry. Only the vocabulary and symbols are to be applied, not the electronics. Any quantitative behavior implied is intended only as a gross approximation.

This diagram is recognizably only a very crude approximation of the components and functioning of the human respiratory system. It is intended as a rough sketch of a very complex pattern that is at present only dimly perceived. It is hoped that this approach will lend clearer insights and raise clearly defined questions. Perhaps further work can then be applied to elaborating and refining this representation to make it even more useful.

Certain basic definitions are necessary before the diagram itself can be discussed.

Figure 5 shows a summing point represented as an open circle. The solid lines with directional arrows represent neural pathways. A, B, C .... are inputs to the summing point which act upon it, as indicated by the associated algebraic sign, so as to produce the actuating signal E (s) = A + B - C .... As was pointed out above, this "sum" should be seen as indicative of direction of effect, not as a precise, algebraic result.

Fig. 6 presents functional neuronal groups to visualize their response to certain of the influences impinging on them. Increasing or decreasing E (s) will produce an increase or decrease, respectively, in C (s), the

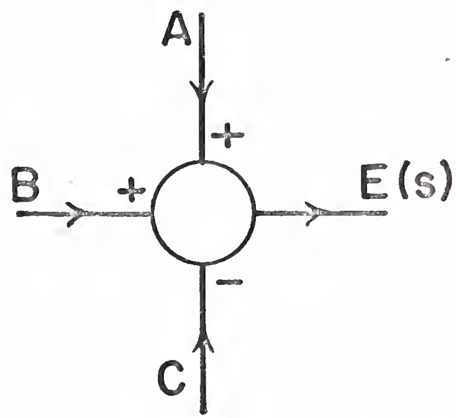


Fig. 5 - Summing Point

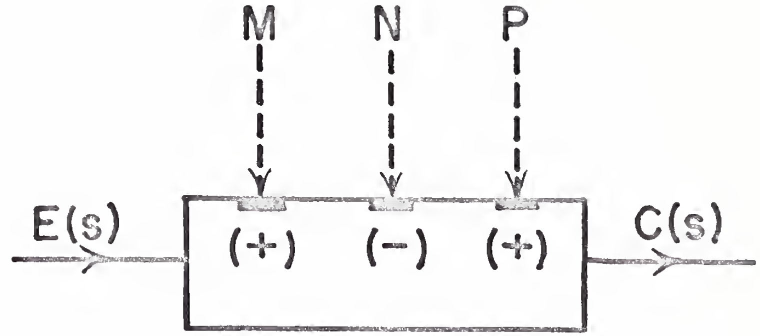


Fig. 6 - Functional Aggregation of Neural Elements

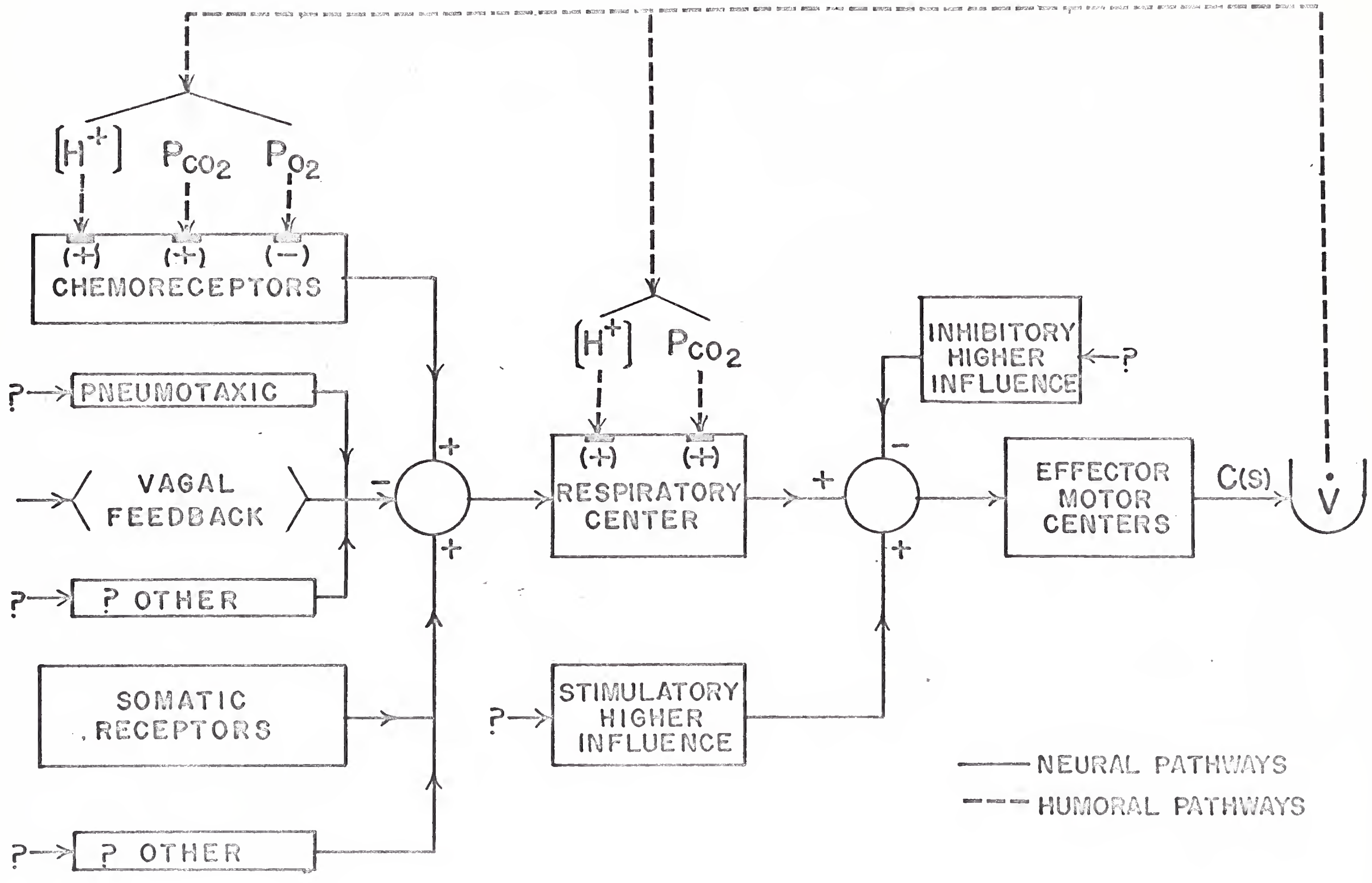


Fig. 7 - Schematic Diagram: Functional Relationships of the Respiratory Center

controlled variable. Nothing more than that is implied. The dotted lines with directional arrows indicate non-neural, humoral pathways. M, N, P .... represent measurable humoral parameters, and their site of action on the "transducer neurons" of the nervous system is indicated by the dark bars, and the algebraic signs beneath each indicates the direction of effect on C (s) produced by increasing M, N, P, etc.

Having thus defined the basic vocabulary, the respiratory center can be diagrammed with its important functional relationships, as in Fig. 7. Only those pathways particularly pertinent to respiration and physical work have been made explicit. Additional factors, known and unknown, are acknowledged but not elaborated.

Using this diagram, it becomes easy to point out that the motor nerve activity C (s) which drives the muscles of respiration to produce a given ventilation, $\dot{V}$, is the result of a multitude of controlling factors. The interplay of these factors is well described by the diagram to support the contention that it is unnecessary to insist that a humoral factor be the principle regulator of respiration in exertion.

However, it has been very difficult to accept that the oxygen and carbon dioxide levels in the milieu interne might have no controlling influence on respiration during exercise. Since the cardinal function of respiration is to acquire oxygen and dispose of carbon dioxide, it would be very rash to propose some completely unrelated mechanism to regulate respiration without first searching for some role for carbon dioxide and/or oxygen. Obviously, it is important to search for humoral factors which may

effect changes in respiration, and which may act at any point of influence.

Thus, it has been demonstrated that raising the hydrogen ion concentration or the P_{CO_2} will increase the output of the respiratory center by direct effect[19]. It has been shown that the aortic and carotid chemoreceptors are sensitive to pH, P_{CO_2}, and P_{O_2}[20]. The feedback loop from $\dot{V}$ is closed via these sensors.

However, it may now be timely to formulate and investigate more fully the alternative pathways for stimulation of respiration.

The many investigations already reported would seem to point to a capacity built in to the system, whose characteristics enable an anticipatory adjustment of ventilation to prevent any change in oxygen or carbon dioxide levels in the circulating blood. Such an extraordinary wisdom cannot be asserted for the body without careful and difficult investigation. It does seem timely to propose it, and to employ the concepts and vocabulary of electronic technology more extensively in investigating it.

W. O. Fenn has speculated on this mode of operation for the respiratory center in the face of exercise, calling it a 'behavioristic approach' to its function[21]. None of this speculation should be construed as minimizing the importance of the chemosensitive mechanisms in homeostasis. In the face of exercise in the intact animal and man these simpler chemical drives seem not to play a dominant role in regulating respiration[22, 23, 24, 25].

A few other details pertinent to humans in exercise are relevant here. Cronin & MacIntosh, 1962, found that muscular efficiency was measurably

greater under conditions of induced hypoxia[26]. This may be related to the increased contractility of actinomyosin in an acid medium. Pulmonary blood volume drops in normal subjects by a mean of 6% during supine exercise for three minutes at 112.5 Kg-M/min[27]. Pulmonary diffusing capacity increases when normals are subjected to moderate to severe degrees of exercise; at mild exercise levels the diffusing capacity may not change. In the face of chronic lung disease, the rise is less, and in most individuals, there was seen to be no change or a fall[28]. Both ventilation and perfusion are greater in the more dependent areas of the lungs, with a higher ventilation to perfusion ratio in the upper lung fields. These findings were not significantly changed in normals by exercise[29]. Oxygen consumption, pulse rate and work load are closely related. The pulse rate may be misleading in those in poor physical training[30].

Working capacity, defined by pulse rate limits of 170/minute, has been studied. This has been shown to increase linearly with age and to be consistently greater in males than females[32,33]. Whereas, studies of the pulse rates in recovery from exercise have not been rewarding[34], several other measurements of exercise in heart disease have been fruitful[35,36].

The development of exercise tests in the evaluation of pulmonary disease has been more limited. Jones et al, 1963, measured the change in FEV produced by exercise and Gandevia, 1963, observed the response of minute ventilation in the last minute of a four minute exercise test[37,38].

Of more specific interest in terms of the present study are the reports of Berg, 1947, Erikson, 1957, and Refsum, 1964[39, 40, 41]. These investigations were concerned with the response to acute exercise, with measurement of oxygen and carbon dioxide curves during the recovery phase. These studies used short exercise regimens of one minute under a moderate to large work load. Results showed a small but definite difference in the different groups under consideration. The overlap with the normal population in all these measurements was considerable. Only 2/3 of Refsum's group of cases fell outside the normal range.

The objectives of this particular study are limited. First it provides a preliminary evaluation of the efficacy of this type of exercise stress test in the study of cardio-pulmonary disease. Second, it can serve, as a pilot study, as a nucleus around which improved a refined exercise tests may develop.

In the face of the paucity of experimental regimens available for the conduct of a test of this kind, it is the purpose of this inquiry to provide a first, gross evaluation of the usefulness of such a test in children with cystic fibrosis. It is hoped that such an effort will help to determine whether or not attempts to polish and refine and perfect such tests might be fruitful in the investigation and treatment of pulmonary disease.

Formal statistical analysis was not brought to bear on the data of the present study, because of the small sample size, because of the inherent coarseness in this context of minute volume measurements,

and because of the large scatter resulting. Carefully designed and executed visual displays of data, described above, are adequate for this purpose.

In all of figures 8 through 13, though a very broad correlation between the presence of pulmonary disease and an elevation in the CO_2 half time can be visualized, it is also apparent that the degree of overlap between the diseased and the normal population is considerable. The lowest 1/2 time was shown by one of the patients (G. A.). He was, also, the youngest individual tested at 5-11/12 years, but his exercise level, 20 Kw, was equal to the work done by the oldest patient in the group (C. McM.), 23-1/12 years old.

For this reason only the very broadest of generalizations can be made regarding the results of this study.

From figures 8 and 9, it is apparent that none of the normals showed half times over 150% of predicted. Among the patients, six of the thirteen plotted fall above 150% of predicted half time. In addition the minimal half time of each of the patient groups is greater the more marked the involvement by disease, though less significance can be attached to such an observation. It is of interest to note that none of the class III 1/2 times fell below 100%.

Cook _et al_ studied 64 patients with cystic fibrosis, age 6 to 25 years[4]. 70% showed an increase, outside of the normal range, of the ratio RV/TLC. Only 46% showed an elevated RV. 34% showed a fall in VC, and 21% an increase in FRC.

In the group of patients studied here, only 46% had elevated RV/TLC. 46%, also, had a % predicted half time of over 150%, but only 33% had both an elevated RV/TLC and an elevated 1/2 time.

In figures 10 through 13, both ordinate and abscissa are plotted linear-linear in percentage deviation from the predicted value concerned. If there were no significant relationship between the disease and the values of the ordinate and abscissa coordinates, the points as plotted should group themselves at random. They would show radical symmetry around the intersection of the ordinate and abscissa 100% lines. If the disease effected only the ordinate quantity, the plot would show an axis of symmetry around the 100% line arising from the abscissa. If both the ordinate and abscissa values were significantly effected by the disease, the points plotted should tend to segregate in one of the quadrants formed by the 100% lines.

In all of these figures, the disease seems to have tended to raise the 1/2 time above that predicted for that age. In fig. 10, the disease tends to elevate the RV/TLC, and the points tend to fall in the upper-right quadrant.

In fig. 11, the disease tends to raise the RV, and the points tend to fall in the upper-right quadrant.

In fig. 12, the vital capacity is decreased in most, and the points tend to fall in the lower-right quadrant.

In fig. 13, the functional residual capacity is decreased in most, and the points tend to fall in the lower-right quadrant.

SUMMARY & CONCLUSION

It should be emphasized again in closing, that the skew seen here may well be produced by factors other than the pathologic pulmonary forces in cystic fibrosis. The size of the normal group is insufficient to ensure that they are in fact completely reliable to represent the normal population with any exactness. The results shown above are not inconsistent with the initial hypothesis that pulmonary disease, and cystic fibrosis in particular, will prolong the time required for the elimination of excess CO_2 resulting from exercise.

The test in its present form is inadequate to provide a definitive and clinically useful laboratory test of pulmonary function. However, it does provide additional evidence that there may be some promise in further development and refinement of the study of the diseased lung under stress.

OVERALL SUMMARY

Twenty subjects, fourteen patients with cystic fibrosis and six normal individuals, were moderately exercised on a bicycle ergometer.

Collections of minute volumes of expired air before, during and following exercise were made.

The times required for the carbon dioxide output to fall half way to the level at rest were calculated.

These times, for cystic fibrosis patients, were compared with the times for normals and with selected objective tests of pulmonary function.

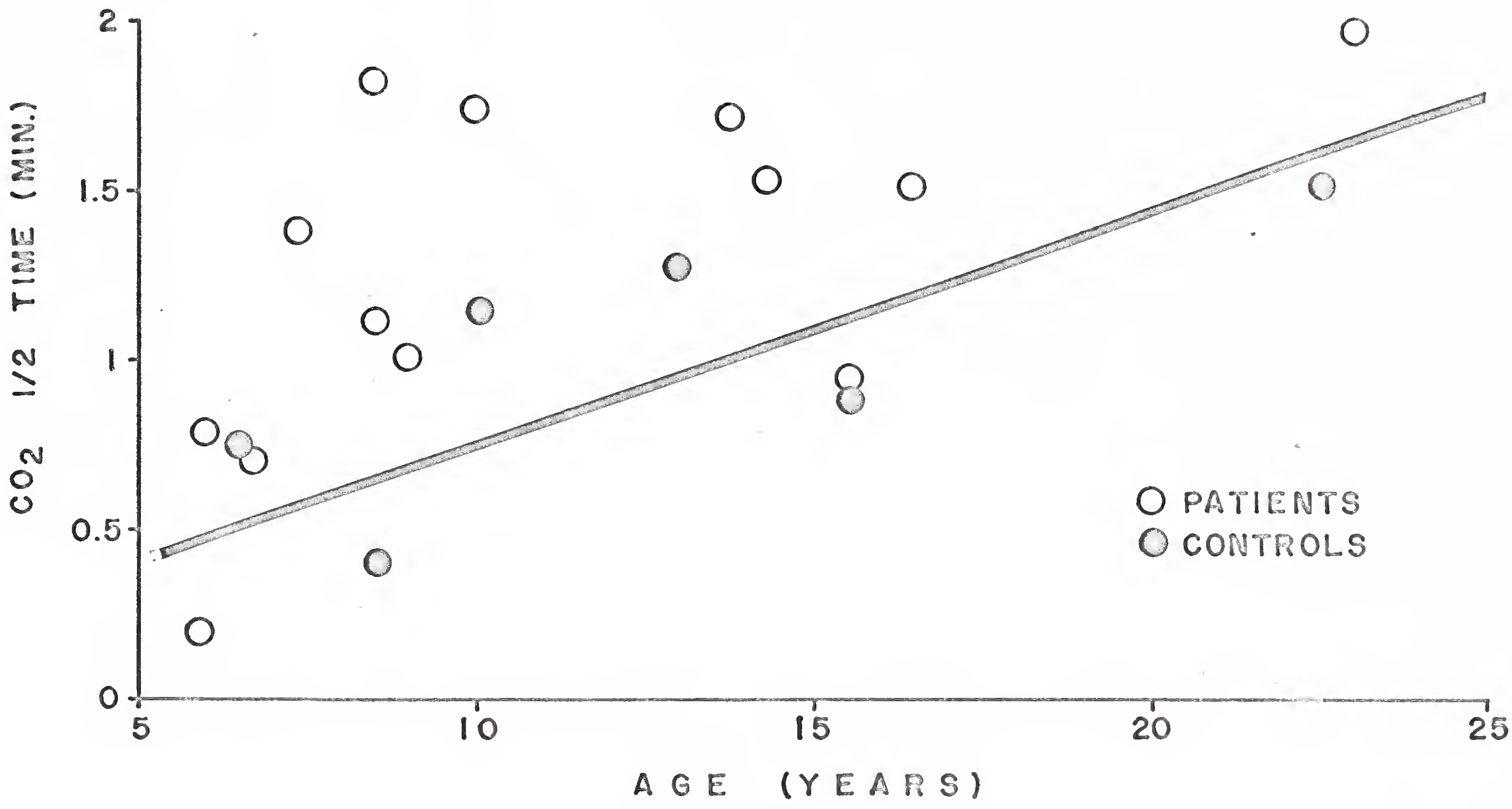


Fig. 8 - Real CO_2 1/2 Time in Cystic Fibrosis & in Normals

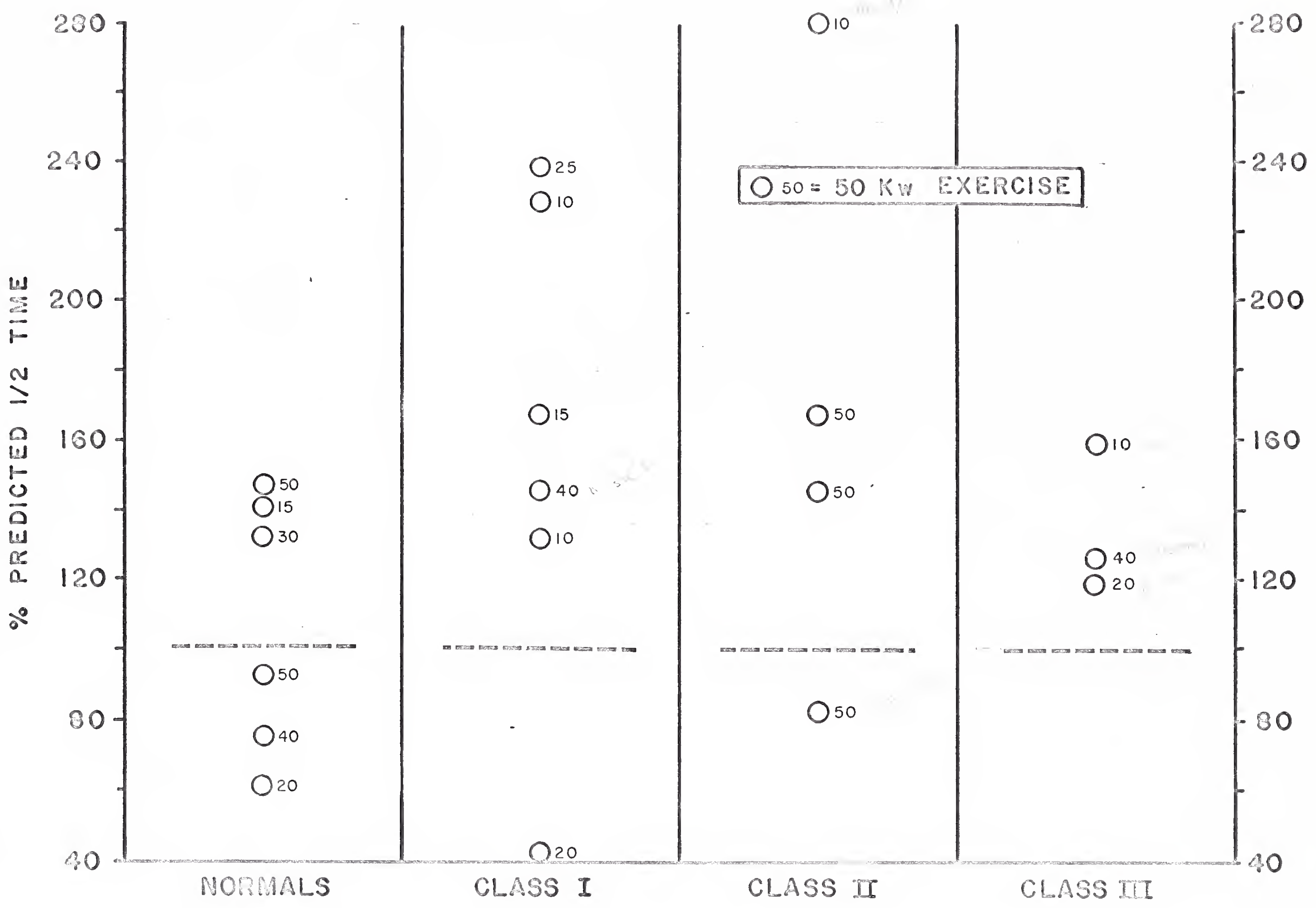
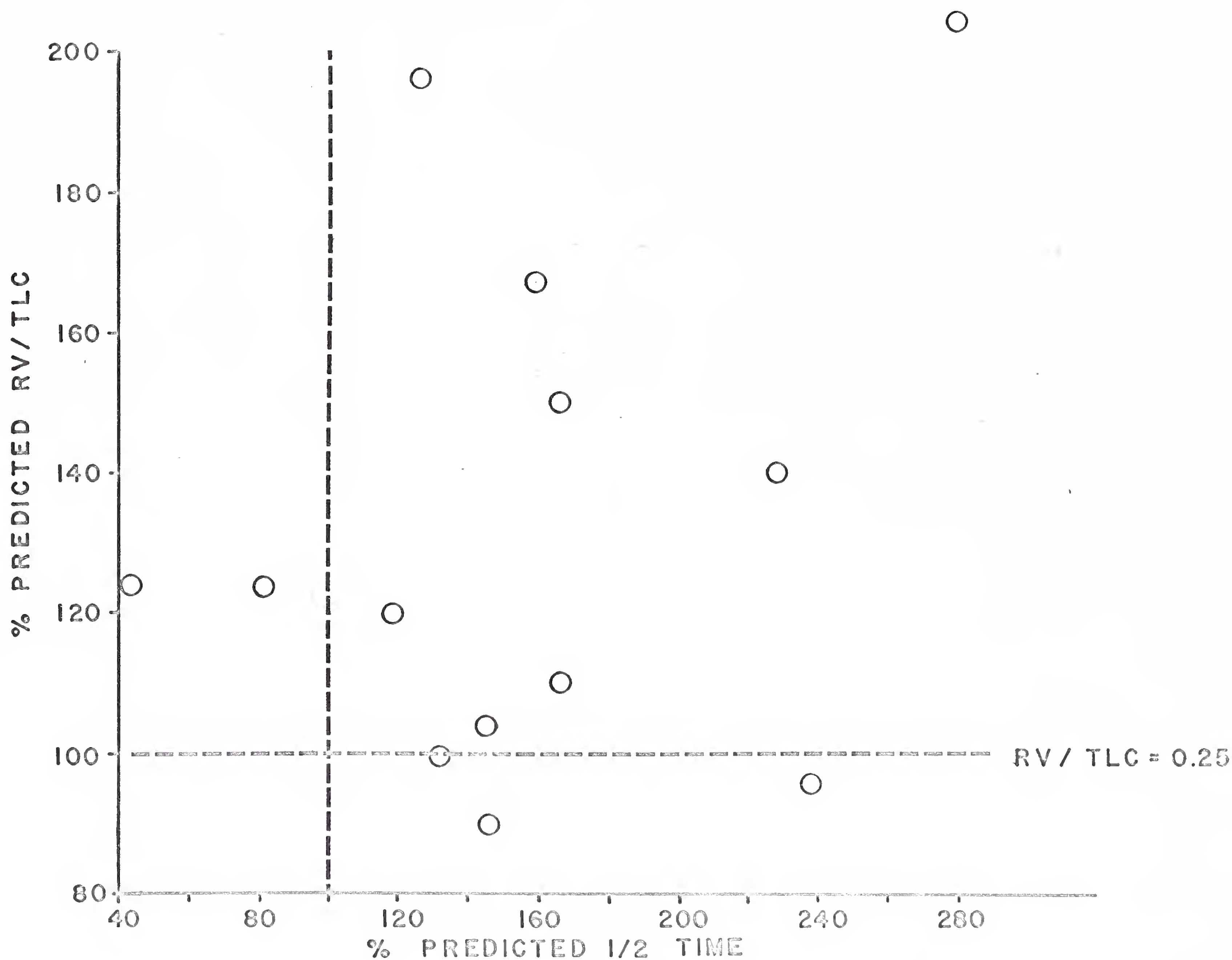


Fig. 9 - Classification According to Physical Activity



200
180
160
140
120
100
80
% PREDICTED RV/TLC
RV / TLC = 0.25
40
80
120
160
200
240
280
% PREDICTED 1/2 TIME

Fig. 10

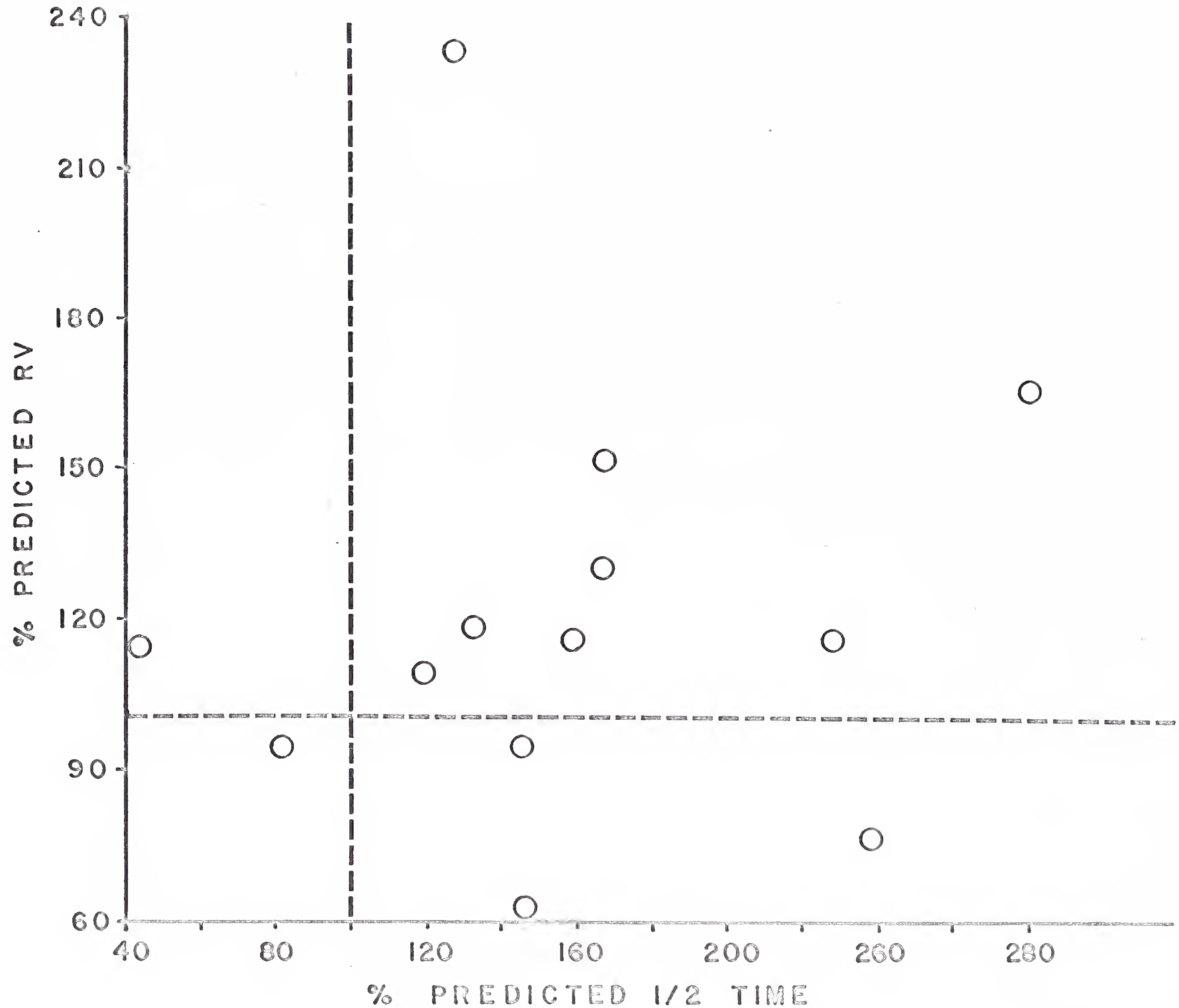

240
210
180
150
120
90
60
% PREDICTED RV
40
80
120
160
200
260
280
% PREDICTED 1/2 TIME

Fig. 11

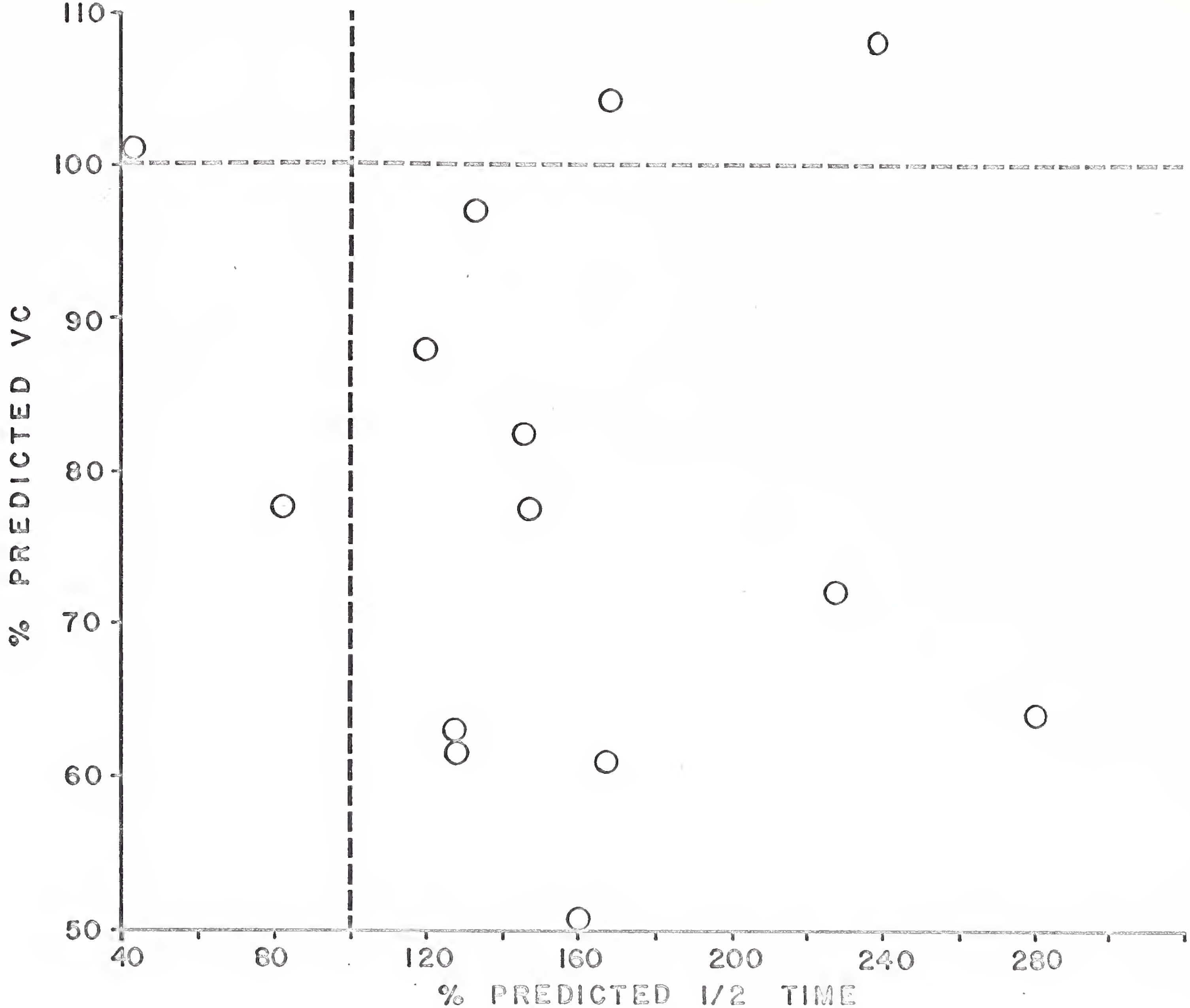

110
100
90
80
70
60
50
% PREDICTED VC
40
80
120
160
200
240
280
% PREDICTED 1/2 TIME

Fig. 12

APPENDIX

Tabulated Data

Patient	Age	Height[1]	Work load[2]	CO_2 ½ time[3]	RV/TLC
G.A.	5 11/12	110	20	0.20	.31
L.L.	6 0/12	128	10	0.78	.42
R.M.	6 8/12	118	10	0.70	.25
M.M.	7 4/12	116	25	1.38	.24
E.S.	8 5/12	123	10	1.82	.51
N.C.	8 7/12	129	15	1.12	.28
S.M.	9 0/12	130	40	1.00	.22
M.L.	9 1/12	127	10	3.50	.44
L.I.	10 0/12	121	10	1.73	.35
D.D.	13 10/12	138	50	1.71	.37
D.R.	14 4/12	161	50	1.51	.26
J.D.	15 7/12	149	50	0.94	.31
J.McN.	16 5/12	161	40	1.50	.49
C.McM.	23 1/12	163	20	1.95	.30

Normal	Age	Height[1]	Work load[2]	CO_2 ½ time[3]	RV/TLC
D.R.	6 6/12	107	15	0.73	
J.A.	8 7/12	121	20	0.39	
D.M.	10 1/12	144	50	1.13	
A.G.	13 0/12	158	30	1.27	
B.L.	15 7/12	153	40	0.88	
B.D.	22 7/12	162	50	1.50	

1: centimeters 2: Kw, see text 3: minutes

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